REMARKS

The invention provides a method of promoting bone marrow cell proliferation by administering unglycosylated, recombinant human alpha-fetoprotein (rHuAFP), produced in a prokaryotic cell (*e.g.*, *E. coli*).

Election/Restriction

Applicant affirms the provisional election made without traverse to prosecute the invention of Group I, claims 19 and 21. Accordingly, claims 1-18 and 22-24 have been canceled as being drawn to non-elected inventions.

Office Action Mailed March 31, 1998

Claims 19 and 21 are pending in the application. Claims 19 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 103(a). Each of these rejections is addressed as follows.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 19 and 22 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. More specifically, the Examiner asserts that the dosage range recited in the specification is too large, and does not enable the skilled artisan to practice the invention because of possible suppressive effects of HuAFP on cells of the immune system at the

upper end of the range.

This concern cannot properly form the basis for a lack of enablement rejection, for several reasons.

In the first place, appropriate dosages of AFP in any given case are readily determined. Of course, optimal dosage will vary from patient to patient, depending on the particular circumstances of their disease. Optimization of the dosage of a drug for a particular disease often involves administration of the drug at high doses, even when these doses have been shown to have adverse effects. For example, cyclosporine is a commonly used systemic immunosuppressant that is known to cause hypertension, nephrotoxicity, and hepatotoxicity at high doses, and may render a patient susceptible to infection and neoplasia (Physician's Desk Reference ("PDR"), 52nd Edition, Medical Economics Company, Inc., Montvale, New Jersey, 1998, pp. 1882-1889; Exhibit A). The PDR provides guidance on how to administer Neoral®, which is an oral formulation of cyclosporine, and how to monitor the side effects of Neoral® administration, and states:

> The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation. . . intersubject variability contributes to the need for individualization of the dosing regimen for optimal therapy. Emphasis added.

Thus, the PDR clearly advises against predetermined doses and, instead, recommends optimizing dosages on an individual basis. It does not follow, therefore, that such optimization constitutes undue experimentation.

Secondly, Applicant emphasizes that HuAFP has no suppressive effects on bone marrow cells, which would be expected to be hypersensitive to immunosuppressive compounds. Indeed, as is discussed at pages 18-19 of the specification, bone marrow cells undergo a strong proliferative response in the presence of recombinant HuAFP. Furthermore, HuAFP suppresses the responses only of a small subset of fully-differentiated mature T-cells. This subset constitutes autoreactive and cytotoxic T-lymphocytes, and not the whole population of T-cells. Administration of HuAFP, therefore, does not affect the function of the majority of cells in the immune system. Since the upregulation of autoreactive and cytotoxic T-lymphocytes may have detrimental effects on the human body, causing a variety of different autoimmune diseases, suppression of these cells cannot be construed as a harmful effect.

As another consideration regarding the effects of HuAFP at high doses, Applicant points out that AFP is a natural substance which is found in large amounts in the human fetus, up to 3000 μg/ml, and up to 500 ng/ml in the bloodstream of pregnant women. [Gitlin, D., 1975, Normal biology of α-fetoprotein. *In* Carcinofetal Proteins: Biology and Chemistry, Hirai, H. and E. Alpert (eds.) pp 7-16, Ann. N. Y. Acad. Sci.; Exhibit B]. Therefore, HuAFP can indeed be present in significant quantities without causing adverse reactions. Accordingly, the Examiner's concern regarding the suppressive effects of recombinant HuAFP is misplaced and this basis of the rejection should be withdrawn.

Furthermore, the Examiner applies a standard of perfection with respect to

enablement that finds no basis in the statute or the case law. The Examiner requires that every embodiment falling within the claims perform successfully and without side effects, with failures in thought experiments in "extreme cases" negating enablement. If this were the standard, generic claims would never be allowable, in any instance in which an Examiner can imagine a single inoperative embodiment. This is not the standard the law requires. For example, in *Application of Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 218 (C.C.P.A. 1976), the Court, in holding that a claimed invention was enabled even though the claims admittedly included inoperative embodiments, stated that "the evidence as a whole, including the inoperative as well as operative examples, negates the PTO position that persons of ordinary skill in this art, given its unpredictability, must engage in undue experimentation to determine which complexes work."

In the present case, even the Examiner would agree that there are dosages within the specified range that are not problematical, and as discussed above, the law does not require that all doses in the specified range be optimal. The patent system, in fact, strongly favors, on public policy grounds, early filing of patent applications, once the invention has been fully conceived and can be broadly enabled, as is the case here. On this basis, as well, the lack of enablement rejection should be withdrawn.

Claims 19 and 21 also stand rejected on the basis that the specification does not provide a working example of administration to a mammal. More specifically, the Examiner disagrees with Applicant that the instant situation is distinguishable from *In re*

Colianni (Paper No. 11, page 7).

Applicant reiterates that the Examiner's reliance on *In re Colianni* is misplaced. In direct contrast to the facts of *Colianni*, Applicant's specification, at pages 19-22, provides specific examples for methods of promoting bone marrow cell proliferation. *Colianni* did not include even one "single specific example of embodiment by way of illustration of how the claimed method is practiced." 195 U.S.P.Q. 152. In addition, unlike *Colianni*, Applicant's specification also provides guidance on dosages useful for promoting bone marrow cell proliferation, thus supplying information over and above a working example.

Claims 19 and 21 also stand rejected on the basis of the Examiner's concern that when administered to a mammal, recombinant HuAFP will encounter not only immature bone marrow cells, but also the fully-differentiated mature T-cells in the bloodstream. This rejection is based on an abstract co-authored by the Applicant (Paper No. 7, pages 6-7), which indicates that fully-differentiated mature T-cells are sensitive to the suppressive effects of HuAFP. The Examiner extrapolates from this observation that the skilled artisan would be unable to establish modes, quantities, and length of HuAFP treatment without incurring deleterious effects.

The Examiner has misinterpreted the abstract co-authored by the Applicant, regarding the suppressive effects of HuAFP on cells of the immune system. As stated above, HuAFP suppresses the responses only of a subset of fully-differentiated mature T-

cells, comprising autoreactive and cytotoxic T-lymphocytes, and not the whole population of mature T-cells. Suppression of these autoreactive and cytotoxic T-cells does not cause deleterious effects; thus the issue of predicting the mode, length, and amount of HuAFP to administer so as to avoid these deleterious effects does not arise. Also, as stated above, administration of a drug known to have deleterious effects, for example, cyclosporine, is not uncommon, and a skilled artisan would be able to avoid such effects without undue experimentation. As is the case with strong medicines like cyclosporine, unpleasant side effects can be expected at very high doses, and may be accepted as part of the cost-benefit analysis in which the physician engages on behalf of a patient.

Applicant points out that "the first paragraph of §112 requires nothing more than objective enablement." *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). As stated in *In re Marzocchi*:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope used in describing and defining the subject matter sought to be patented must be taken in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The Examiner's speculative basis for rejecting the claims is a far cry from the evidentiary- or scientifically-based reasoning on which objective truth or accuracy of the specification may be questioned.

Applicant respectfully requests that the Examiner reconsider and withdraw the rejections under § 112, first paragraph.

Rejection under 35 U.S.C. § 103(a)

Claims 19 and 21 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hoskin et al. (1985). The Office Action (at page 4) states:

> The prior art is equivocal: '...the role of sialic acid in the immunological activity of AFP remains contentious. It is equally possible that the immunoregulatory function of AFP is determined by primary structure rather than by posttranslational modification.' (Hoskin et al., 1985, page 164). Based upon these factors, it would appear that glycosylation of AFP is immaterial to its function, and thus AFP taught in the prior art is functionally equivalent to that of the instant specification,...

The Examiner's argument is apparently based on an incomplete reading of Hoskin et al. Hoskin does not even mention a recombinant HuAFP, much less indicate that the normally heavily glycosylated AFP might be biologically active in an unglycosylated state, as is required by claim 19. Indeed, in contrast to the Examiner's statement, the cited Hoskin passage clearly implies that glycosylation is material to the function of AFP. More specifically, the sentence previous to the one quoted by the Examiner states that "...deglycosylated murine AFP molecules are reported to lack lymphosuppressive activity." (emphasis added). A fair reading of this passage is that glycosylation is most likely very important for the biological functions of AFP. Thus, it is clear that prior to the instant invention, the function of glycosylation in AFP was at best uncertain. Applicant's

experiments, as described on pages 16-19 of the specification, were therefore required to demonstrate that unglycosylated AFP retains biological function in the claimed methods. Because Hoskin et al. cannot have taught what they did not know, their article cannot render the claimed invention obvious. Applicant requests reconsideration and withdrawal of the § 103(a) rejection.

CONCLUSION

Applicant submits that all of the claims are now in condition for allowance, which action is respectfully requested. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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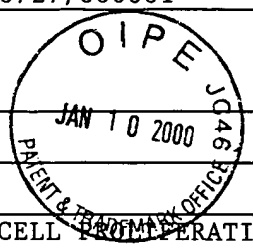

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